Efficacy Biomarkers:
Efficacy/Risk Assessment

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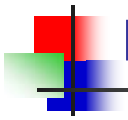
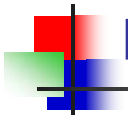
Outline

- History of Safety and Efficacy (= Risk and Benefit)
  - Progression towards individualized therapy
- Examples of risk/benefit changes when the population changes
- Future directions



History of Risk and Benefit



FDA Approval Standard

- Safety: FD and C Act (1938)
  - Drugs should be *safe for their intended use* and studied for safety by "all tests reasonably applicable"
    - Implies risk/benefit analysis
- Efficacy: Section 505 (1962)
  - Need "substantial evidence" of efficacy, that must be derived from "adequate and well-controlled studies
  - Conclusion of 'experts': Drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof

Assessment of Risk/Benefit

- Information on both safety and efficacy needs to be assessed by 'experts' (precisely how to do the assessment not specified)
- Labeling important to give needed information to physicians to assure appropriate balance

Age of Individualization

- Populational responses do not always predict individual responses
- Recognition that the balance of risk and benefit can be altered by:
  - New information about safety post-approval due to larger patient exposure
  - New safety and efficacy data as a result of use of product by patients other than those exposed pre-approval

Safety and Efficacy by Gender, Age and Race

- CFR-Mandated analyses
  - 'Geriatrics' section in labeling
- ICH E7 Geriatrics Guidance
- FDA Guidance on Collection of Race and Ethnicity data (Sept 2005)

ICH E3: 'Clinical Study Report'

'The efficacy and safety results of the study and the relationship of risks and benefit should be briefly summarized and discussed...'

'Any specific benefits or special precautions required for individual subjects or at-risk groups and any implications for the conduct of future studies should be identified'

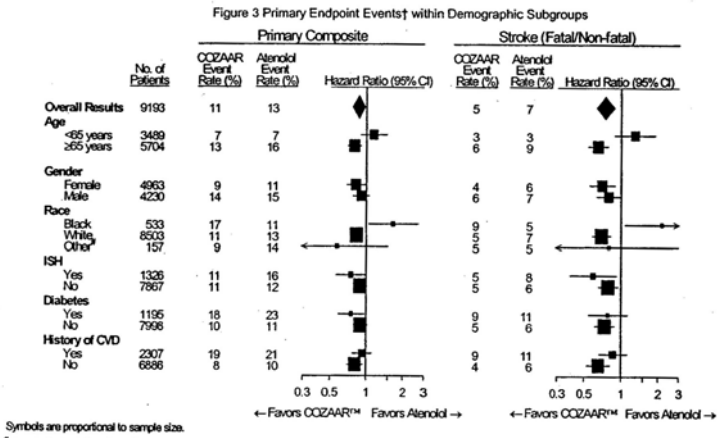
E4 'Dose-Response'

- "Any given dose provides a mixture of desirable and undesirable effects, with no single dose necessarily optimal for all patients"

Examples of populations with altered Risk/Benefit Calculus

- Efficacy:
  - Inhaled Nitric Oxide for Respiratory Failure
    - Neonates: improved oxygenation and reduced need for ECMO
    - Adults: improved oxygenation but no reduction in time on ventilator
  - Losartan c/w Atenolol after MI
    - LIFE Trial

Figure 3 Primary Endpoint Events† within Demographic Subgroups



Symbols are proportional to sample size.

*Other includes Asian, Hispanic, Asiatic, Multi-race, Indian, Native American, European.

†Adjusted for baseline Framingham risk score and level of electrocardiographic left ventricular hypertrophy.

Examples of populations with altered Risk/Benefit Calculus

- Safety:
  - ASA and Gender:
    - Women: increased risk of cerebral hemorrhage (also decreased efficacy?)
  - Populations identified by:
    - Drug Interactions (e.g., CYP 3A4)
      - Cisapride, terfenidine
    - Chronicity of Use
      - Primary prevention vs. Treatment
      - COX2s?

ICH E2e: Risk is not static

- The decision to approve a drug is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labeling.
- This decision is based on the information available at the time of approval.
- ...the safety profile of the product can change over time through expanded use in terms of patient characteristics and the number of patients exposed.

Summary

- Clear that populations differ wrt safety and efficacy in ways that are:
  - Hard to predict
  - Often difficult to detect using standard trial databases
  - Changes as populations exposed change
- Important to include these data labeling when known
- Use of population data to identify individual responses and overall risk/benefit is important, but often imprecise and inefficient

What's Required to Further Individualization of Risk/Benefit?

- Regulatory framework for discussion
- Mechanisms to promote needed additional research
- DATA
  - Clear role for biomarkers of all kind, including genomic biomarkers:
    - Provide link between pre-clinical observations and individual patient responses
    - Improve efficiency of data collection and interpretation in drug development

Regulatory Framework

- Guidance: Genomic Data Submissions (2003)
  - Combined meetings with EMEA
- Agency Critical Path WG
  - Promote needed additional research on:
    - Methods
    - Data collection and analysis

FDA Critical Path WG

- Agency-level WG
  - Coordinate cross-cutting activities, assist Center-specific activities
  - Expertise in 'mechanics' of FDA partnership
    - CRADAs, MOUs, Contracts (small)
  - Partnership for large, cross-Agency issues
- Potential Types of Interactions:
  - FDA and Academic Partnerships
  - FDA and Private/Industry Partnerships
  - FDA and NIH Partnerships
  - FDA and other entities (e.g., other government, non-profit)

Suggestion

- Accomplishing this will require extensive collaboration across many stakeholders
  - No one entity has all the needed resources
- Strong need to invigorate careful biomarker characterization to maximize:
  - The efficiency of medical product development
  - The best uses of new medical products for individuals

Pharmacogenomics Guidance on Risk/Benefit

- The promise of pharmacogenomics lies in its potential ability to identify sources of inter-individual variability in drug response (both efficacy and toxicity); *this will help individualize therapy with the intent of maximizing effectiveness and minimizing risk*

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